PENETRATION OF CEFOPERAZONE INTO THE VENTRICULAR FLUID IN PATIENTS WITH NON-INFLAMED MENINGES

by

Mary Elizabeth Gross

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University of Utah in partial fulfillment of the requirements
for the degree of

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY

I have read the clinical research project of Mary Elizabeth Gross in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

June 2, 1982
Date

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Chairman

Approved for the Doctor of Pharmacy Committee

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

Mary Elizabeth Gross

We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

June 2, 1982
Date

Chairman, Supervisory Committee

June 2, 1982
Date

Member, Supervisory Committee

June 2, 1982
Date

Member, Supervisory Committee

June 2, 1982
Date

Member, Supervisory Committee

June 2, 1982
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Member, Supervisory Committee

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INTRODUCTION

Hydrocephalus is characterized by an abnormal accumulation of fluid within the cranial vault. This results from an increased pressure gradient between the intraventricular fluid and the brain due to the inadequate removal of this fluid by the lymphatic, circulatory, and central nervous systems. Possible etiologies of this disorder include: (1) congenital malformation; (2) excess formation of cerebral spinal fluid by the choroid plexus, which may or may not be accompanied by abnormal absorption of the fluid into the vascular system; (3) cysts and neoplasms involving the brain; (4) infections within the central nervous system; and (5) trauma. Clinical signs and symptoms of hydrocephalus include an increase in the intracranial pressure, enlargement of the cranium, headaches, vomiting, confusion and lethargy.

Intracranial pressure is regulated by the rate of formation and the resistance of the arachnoid villi to absorb the fluid. Normal cerebral spinal fluid pressure is between 70 to 180 mmH_2O. With hydrocephalus, this pressure may increase to 400 to 600 mmH_2O. If this condition is left untreated, the resultant increase in fluid pressure may lead to atrophy of the brain, mental deterioration or convulsions.[2] Surgical placement of ventriculo-peritoneal (VP) shunts are used in patients with hydrocephalus to relieve the elevated intracranial pressure, by providing a route for removal of the excess fluid.

A major complicating factor which contributes to the morbidity

same study, it appeared that patients who received prophylactic antibiotic therapy directed at staphylococci had a lower incidence of infection. The results of this and other similar studies have led to the use of antimicrobial prophylaxis perioperatively during shunt placement procedures.[3,7-9,12-16] Ampicillin, methicillin, nafcillin and trimethoprim-sulfamethoxazole have been used in this institution.* Prevention of infection should lead to decreased hospitalizations, decreased number of shunt revisions, and a decrease in the overall morbidity and associated mortality. It is therefore desireable to treat the patient prophylactically with an antibiotic that will be active against the primary organisms involved.

Cefoperazone (Cefobid,® Pfizer Pharmaceuticals), which is structurally related to cefamandole and piperacillin (Figure 1), is a semisynthetic cephalosporin for parenteral use. Like other beta-lactam antibiotics, cefoperazone inhibits cell wall synthesis by inhibiting the transpeptidase enzyme, which prevents the splitting of the peptide bond between the two terminal D-alanine residues of each polypeptide side chain.[17] *In vitro*, cefoperazone is relatively resistant to beta-lactamase induced hydrolysis. *In vitro* and *in vivo* data have shown this agent to be active against both gram positive and gram negative organisms, including staphylococcus sp., *Escherichia coli*, pseudomonas sp., klebsiella sp., proteus sp., and *Haemophilus influenzae*.[18,19]

Cefoperazone elimination follows a two-compartment model, with a rapid distribution phase (6.6 ± 3.1 minutes).[20,21] The elimination half-life has been reported to be 1.6 to 2.05 hours in healthy subjects

*Primary Children's Medical Center, Salt Lake City, Utah.

after intravenous administration.[18] High pressure liquid chromatography studies have detected degradation products of cefoperazone.[22] Activity of these metabolites has not been reported to date. The apparent volume of distribution of cefoperazone in healthy subjects has been reported as 9.4 to 14.5 liters in the adult, and 0.5 liters per kilogram in the newborn infant.[18,21,23] Cefoperazone has been found to have a protein binding capacity of approximately 90 percent to human albumin.[18,23,24]

Penetration into the cerebral spinal fluid (CSF) has been reported in rabbits with inflamed meninges, following a single dose infusion of cefoperazone at 25 mg/kg. The CSF levels were found to be between 4.2 and 8.2 percent of the concurrent serum concentration.[25] This agent penetrates into the CSF in pediatric patients with bacterial meningitis and Anderson et al. have reported CSF concentrations of cefoperazone ranging between 1.8 to 3.7 mcg/ml in newborn infants (range 4 to 26 days) with noninflamed meninges.*

Cefoperazone generally has been well tolerated following parenteral administration. Adverse effects in 21 of 756 patients treated with cefoperazone in clinical trials in Japan have been reported.[26] The most commonly reported side effects included rash, diarrhea, fever, dizziness, chills, headaches, and vascular pain following intravenous injection. Abnormal laboratory results were seen in an additional 21 patients. These included transient elevations of serum transaminases, alkaline phosphatase, and eosinophilia.

Cefoperazone, with its broad spectrum of activity, apparent

*Donald Hilligos, Pharm.D., Assistant Professor of Clinical Pharmacy West Virginia University, personal communication, May 1982.

ability to penetrate into the central nervous system, and low incidence of side effects, may represent an alternative to the present antibiotic regimen used for prophylaxis in VP shunt procedures.

OBJECTIVES

The objectives of this study were to determine simultaneous serum and ventricular fluid levels and side effects of cefoperazone in children with non-inflamed meninges requiring perioperative antibiotic prophylaxis for placement or revision of a VP shunt. The ventricular fluid levels obtained were then compared to the *in vitro* concentrations required to inhibit bacterial growth of the most common organisms associated with VP shunt infections.

MATERIALS AND METHODS

Subject Selection

Five subjects requiring perioperative antibiotic prophylaxis for placement, or revision, of a VP shunt were selected for the study. Three of the subjects underwent surgery for placement of the VP shunt for the first time. Patient characteristics are listed in Table 1. There were three males and two females with an average age of 7.5 months (range 6 days to 30 months). Subject number one was reentered into the study three months after the initial placement of the VP shunt for revision of the shunt, as subject number four. Suitability to participate in the study was determined by medical history and physical examination performed by the physician co-investigator. Objective evaluation was completed by a battery of laboratory tests (complete blood count with differential and reticulocytes, prothrombin time, liver function tests, serum creatinine, and complete urinalysis).

Exclusion Criteria

The following exclusion criteria were used: (1) subjects with evidence of renal disease indicated by a serum creatinine greater than 1.5 mg/dl; (2) subjects with evidence of hepatic disease indicated by a serum glutamic oxaloacetic transaminase greater than 50 IU/L, a serum glutamic pyruvic transaminase greater than 50 IU/L, or a gamma glutamyl transpeptidase greater than normal as determined by the subject's age; (3) subjects with a documented history of an allergic reaction to cephalosporin antibiotics; (4) subjects with a history of an anaphylactoid reaction to penicillin antibiotics; (5) subjects less than 38 weeks of gestational age; (6) any subject within 14 days of the initial diagnosis of inflamed meninges; and (7) subjects' parents or guardians who declined to sign the study consent form.

Study Design

The study was an open, noncomparative trial of a single dose of cefoperazone, which was administered in conjunction with the antibiotics routinely administered (ampicillin, methicillin, or trimethoprim-sulfamethxazole) for perioperative prophylaxis of VP shunt placement or revision. Subjects were divided consecutively into two groups designated A and B. Group A participants received 50 mg/kg of cefoperazone, while subjects in group B received 100 mg/kg. This change in dosage was due to clinical data received by the sponsor* indicating the safety and efficacy of the higher dose. Baseline laboratory values were obtained no less than 48 hours prior to administration of the agent. Blood pressure, heart rate, temperature, respiratory rate,

*Pfizer Pharmaceuticals, New York, New York.

the presence or absence of lethargy and irritability, and the appearance of the injection site were recorded prior to the infusion of cefoperazone. A two milliliter blood sample was obtained prior to the administration of the agent. This sample served as a blank. The sample was centrifuged at 5000 rpm for five minutes to separate the plasma from the cells. The plasma was decanted into a glass tube and promptly frozen at -70° C. Each subject then received one dose of cefoperazone (50 mg/kg or 100 mg/kg), which was infused over one to two minutes prior to the subject being called to the operating room, with one exception. Neither the resident nor the phlebotomist were able to start the I.V. prior to subject number five being transported to the operating room. Consequently, the cefoperazone was administered in the operating room by the anesthesiologist. A four milliliter sample of the ventricular fluid sample was obtained at the time of shunt placement. Half of this sample was sent for gram stain, culture, cell count, and glucose and protein determination. In addition, a two milliliter blood sample was obtained by the physician at a site other than the original cefoperazone injection site at a time as near to the drawing of the ventricular fluid as was feasible during the surgical procedure. The blood sample was taken to the laboratory and centrifuged at 5000 rpm for five minutes to separate the plasma from the cells. The plasma was then decanted into a glass tube. Both the ventricular fluid and serum samples were then promptly frozen at -70° C. The samples were analyzed within four months of collection. Samples remain stable for a minimum of one month if thawing is avoided.*

*Marvin Meyer, Ph.D., Professor, Assistant Dean, College of Medicine, University of Tennessee, personal communication, May 1982.

Subjects were monitored for adverse effects for 24 to 48 hours after the administration of cefoperazone. The time of onset, duration, and severity of side effects were recorded. Follow-up laboratory studies were performed between 12 to 24 hours after the administration of cefoperazone.

Cefoperazone Assay

The cefoperazone assay was performed by Dr. Marvin Meyer at the University of Tennessee. A gradient high pressure liquid chromatography (HPLC) procedure was used for the determination of the amount of cefoperazone in human serum and CSF. This assay adequately separated cefoperazone from other antibiotics and cefoperazone degradation products. The sensitivity of the assay for the serum was less than five mcg/ml and less than one mcg/ml for the CSF. The coefficient of variation was less than 5.5 percent.

RESULTS

In group A subjects there were no concomitant serum samples available for analysis (Table 2). In two subjects (number one and three), the CSF levels were 0.2 mcg/ml and 0 mcg/ml at 120 and 185 minutes after the dose respectively. The mean time between drawing the CSF and serum samples for the subjects in group A was 11 minutes (range 7 to 25 minutes).

Ventricular fluid and serum samples were analyzed for the three subjects in group B (Table 3). Cefoperazone was detected in the CSF of two subjects (four and six). The CSF concentrations were 7.5 mcg/ml and 3.2 mcg/ml, respectively. The percentage of cefoperazone in the CSF compared to the serum were 2.35 percent and 1.64 percent,

respectively. No cefoperazone was detected in the CSF in subject five, while the concurrent serum concentration was 247.7 mcg/ml. The mean time between drawing of the CSF and serum samples for group B was 15.3 minutes (range 10 to 23 minutes).

All gram stains and cultures of the CSF for all subjects were negative after 72 hours. The CSF cell counts and glucose and protein levels did not suggest the presence of inflamed meninges in all but subjects four and six (Table 4). Monitoring parameters were not altered after the administration of a single dose of cefoperazone (Table 5). Subject one experienced one episode of diarrhea 24 hours after the dose was administered. This same subject had experienced diarrhea prior to the infusion of cefoperazone. Subject two complained of a headache, which required treatment with 60 mg of acetaminophen, nine hours after receiving the cefoperazone. The staff could not associate the headache as an adverse effect versus pain at the site of incision. The complete blood count was normal in all subjects, except for subject six who demonstrated a rise in eosinophils from 3 to 15 percent (Table 6). Subjects one, three, five and six demonstrated a mean reduction in reticulocytes of 59.7 percent (range 47.8 to 71.4%), a mean decline in red blood cells of 18.4 percent (range 9.5 to 31.6%), and a mean reduction in hematocrit of 20.9 percent. The reticulocyte counts remained within the normal range for those subjects as determined by their age.[27]

Subject three demonstrated a slight increase in liver function tests, though the values remained within the normal range. No changes in liver function tests were noted in the remaining subjects (Table 7). Urinalysis remained unchanged in all subjects (Table 8). Follow-up laboratory tests could not be obtained in subject number two due to

refusal of the mother to allow the samples to be drawn.

DISCUSSION

The samples obtained from group A subjects could not be used in the evaluation of the study because the initial assay procedure was not sensitive enough to measure the small quantity of cefoperazone in the CSF. In the process of concentrating the samples, the drug was degraded, invalidating the data obtained. Cefoperazone was detected in the CSF sample of subject one after at least one thawing, suggesting that the penetration into the CSF does occur. Thawing has been shown by Meyer to result in approximately 50 percent degradation of the sample.* These subjects (group A) were retained in the study to note any adverse effects incurred or alteration of laboratory tests demonstrated.

Penetration of the cefoperazone into the CSF was noted in two of the three subjects in group B. Cefoperazone was not detected in the CSF prior to 40 minutes after the administration of the agent. Interpatient variability of both serum and CSF levels was demonstrated. This variability is consistent with the data reported in three newborn infants with non-inflamed meninges, in which the peak serum levels ranged from 133 to 214 mcg/ml. The CSF levels of cefoperazone ranged from less than one mcg/ml to nine mcg/ml.[22] The delay in penetration suggested by the group B subjects may be related to the extensive protein binding of cefoperazone. The concentration of cefoperazone in the CSF may have been altered by the enlarged ventricles detected by computer axial tomography (CAT) scan in the three subjects

*Marvin Meyer, Ph.D., Professor, Assistant Dean College of Medicine, University of Tennessee, personal communication, May 1982.

in group B at the time of surgery. Hydrocephalic patients often have enlarged ventricles, which may alter the volume of distribution of the antibiotic administered. McCullough et al. demonstrated an inverse relationship between ventricle size and the concentration of nafcillin in the CSF.[28] The increased protein and white blood cells in the ventricular fluid in subjects four and six suggest an alteration of the meninges, which may have been seen due to the penetration of cefoperazone into the CSF in these two subjects. In subject four, the original shunt had been fused to the choroid plexus. Upon removal of the shunt, there may have been an influx of serum accounting for higher levels of glucose, blood cells, and cefoperazone. Subject six underwent shunt placement 14 days prior to the procedure in which the cefoperazone was administered. The CSF protein count has been increased in subjects who have undergone recent neurosurgical procedures. In both subjects, the meninges may have been altered, despite negative cultures and gram stains, which would influence the penetration of cefoperazone into the CSF.

Diffusion of antibiotics into the CSF has been considered desirable for antimicrobial prophylaxis against infection in ventriculoperitoneal shunt procedures. Presently, ampicillin, methicillin, nafcillin, and trimethoprim-sulfamethoxazole are utilized in this institution. Penetration into the CSF for each of these agents is limited in the absence of inflamed meninges. Other factors which influence the ability of antibiotics to penetrate into the CSF include lipid solubility, molecular size and structure, and degree of ionization at physiological pH, and active transport mechanisms.[31] The mean CSF concentration of ampicillin was determined in 44 patients in

10 days after the initial diagnosis and initiation of treatment for bacterial meningitis.[29] The concentration of ampicillin was noted to decrease through the course of therapy, as the inflammation subsided. The mean concentration of ampicillin in the CSF at day 10 was 0.8 mcg/ml (range less than 0.03 to 5.9 mcg/ml). This study also demonstrated no correlation between the clinical outcome of each patient and the antibiotic level achieved in the CSF. Peak CSF concentrations of methicillin have been determined in five patients with non-inflamed meninges to range between 0 to 0.69 mcg/ml.[30] In bacterial meningitis, the maximum concentration of methicillin detected has been 2.8 mcg/ml.[30,31] The mean CSF concentration of nafcillin has been determined in eight patients with no evidence of inflamed meninges.[32] The mean peak concentration was 0.12 mcg/ml (range 0.03 to 0.17 mcg/ml). This peak occurred two hours after the end of the infusion. The penetration of trimethoprim (TMP) and sulfamethoxazle (SMX) were determined on four patients with inflamed meninges.[33] The mean concentration of TMP was 1 mcg/ml (range 0.7 to 1.4 mcg/ml) and that of SMX was 4.5 mg/dl (range 1.7 to 8.2 mg/dl). It appears that the concentration of the antibiotic in the CSF is often less than the minimum inhibitory concentration for the pathogen involved (Table 9).[29,31,34,35] However, these agents have been utilized successfully, both in the management of bacterial meningitis and as prophylactic antimicrobials in shunt procedures.[8,9,14-16,29-31,33,36,37] In this study, the concentration of cefoperazone in the CSF in one subject appears to be adequate to achieve the minimum inhibitory concentration for 90 percent of the isolates for the common VP shunt pathogens, if the meninges were not altered (Table 10).[38] Further studies will be necessary to determine

the effective concentration of cefoperazone in the CSF to prevent VP shunt infections.

Adverse effects were minimal in this study population. The eosinophilia reported in one subject is not uncommon.[18] The mechanism is not understood at this time. The mild increase in liver function tests as noted in one subject has also been reported. Previous studies have indicated that this alteration is usually transient in nature.[18] This subject was not monitored beyond 24 hours, as his values remained within the normal limits.

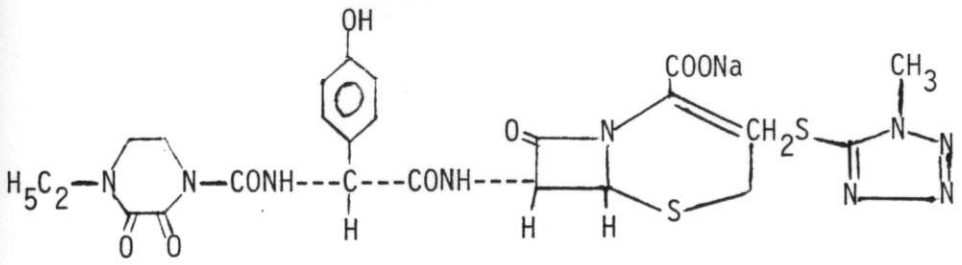
A decrease in reticulocytes, which remained within the normal limits, was observed in four subjects. This was associated with a concurrent decrease in hematocrit and red blood cell count. Further multi-dose studies will be needed to determine the clinical significance of this adverse effect.

CONCLUSION

Cefoperazone is a new semisynthetic cephalosporin with a broad spectrum of antimicrobial activity. This agent appears to penetrate into the CSF in children with non-inflamed meninges and may be an alternative to the present antibiotic regimens used in patients requiring perioperative prophylaxis for shunt placement or revision. Further double-blind trials will be necessary to evaluate the efficacy of cefoperazone as a prophylactic agent in VP shunt procedures. Additional studies to address the severity of the decreased reticulocyte count demonstrated in four subjects in this study will be necessary.

FIGURE

Figure 1. Structure of cefoperazone.



TABLES

TABLE 1. PATIENT CHARACTERISTICS.

Patient	Age at Time of Procedure	Gender	Height (cm)	Weight (kg)	Clinical Diagnosis	Previous Shunt
Group A						
1	6 days	Male	51	3.62	Hydrocephalus post myelomeningocele repair	No
2	30 months	Female	87	11.80	Dislodged VP shunt	Yes
3	6.5 months	Male	67	5.27	Hydrocephalus at birth	No
Group B						
4	3 months	Male	64	6.68	Obstructed VP shunt	Yes
5	10 days	Female	50	2.69	Hydrocephalus post myelomeningocele repair	No
6	5 months	Male	48	2.81	Hydrocephalus - porencephalic cyst	Yes

VP - ventriculo-peritoneal

TABLE 2. CONCENTRATION OF CEFOPERAZONE IN SERUM AND VENTRICULAR FLUID, GROUP A.

Patient	1	2	3
Pre-dose serum concentration (mcg/ml)	-[a]	-	-
Ventricular fluid concentration (mcg/ml)	0.2	-	0.0
Concomitant serum concentration (mcg/ml)	-	-	-
Time of sample after administration (minutes)	120	-	185

a - no sample available for evaluation

TABLE 3. CONCENTRATION OF CEFOPERAZONE IN SERUM AND VENTRICULAR FLUID, GROUP B.

Patient	4	5	6
Pre-dose serum concentration (mcg/ml)	0.0	0.0	0.0
Ventricular fluid concentration (mcg/ml)	7.5	0.0	3.2
Concomitant serum concentration (mcg/ml)	319.5	247.2	195.7
Time of sample after administration (minutes)	120	27	40
Percent penetration into CSF	2.35	0	1.64

TABLE 4. VENTRICULAR FLUID DATA.

Patient	1	2	3	4	5	6
Appearance	sl. hazy/ colorless	clear/ colorless	sl. hazy/ colorless	turbid/ red	clear/ colorless	clear/ yellow
WBC/MM^3	1	0	3	57	1	149
PMN's (percent)	0	0	0	17[a]	0	43[b]
Lymphocytes (percent)	0	0	0	76	0	38
Erythrocytes/MM^3	247	2,000	704	70,000	1	69
Other (percent)	-	-	-	monos - 3 eos - 4	-	monos - 19
Protein (mg/dl)	55	QNS	18	60	46	1,415
Glucose (mg/dl)	34	85	49	207	92	40
Ventricular fluid gram stain	neg.	neg.	neg.	neg.	neg.	neg.
Ventricular fluid culture	NG	NG	NG	NG	NG	NG

PMN's - polymorphonuclear leukocytes
monos - monocytes
eos - eosinophils
NEG. - negative
NG - no growth for 72 hours

a - 16% neutrophils, 1% bands
b - 34% neutrophils, 9% bands
QNS - quantity not sufficient
sl. hazy - slightly hazy

TABLE 5. PRE AND POST CEFOPERAZONE SUBJECT MONITORING PARAMETERS.

Patient	1		2		3		4		5		6	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Temperature (degrees Celsius)	36^{9}ax	37^{7}ax	36^{7}r	37^{8}r	37^{7}r	37^{9}r	36^{6}ax	37^{0}r	37^{5}r	37^{4}r	36^{1}ax	36^{7}ax
Pulse (beats/minute)	144	136	76	98[a]	140	152	166	150	142	160	136	140
Respiratory Rate (breaths/ minute)	44	44	22	30[a]	32	52	16	42	42	48	38	32
Blood pressure (mmHg)	80/P	60/P	96/60	102/78[a]	90/68	100/60[a]	108/P	78/P	65/P	72/P	80/P	92/P
Irritability	-	-	+	-	++	+	++	+[c]	-	-	+	-
Lethargy	-	-	AL/AC	AL/AC	AL/AC	AL/AC	AL/AC	AL/AC	-	-	d	-
Infusion site	clear	clear	clear	clear	clear[b]	clear	clear	clear	clear	clear	clear	clear
Other	diarr.	diarr.	-	H.A.	-	-	-	-	-	-	-	-

a - crying at time of evaluation
b - initial infusion resulted in infiltration due to the technique of administration
c - head discomfort
d - responded to stimuli lethargically
H.A. - headache
ax - axial temperature
r - rectal temperature
clear - without erythema or inflammation
diarr. - diarrhea
AL/AC - alert and active

TABLE 6. PRE AND POST CEFOPERAZONE COMPLETE BLOOD COUNT RESULTS.

Patient	1		2		3		4		5		6	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Hemoglobin (g/dl)	20.7	13.7	14.1	-[b]	15.9	14.4	11.7	9.2	14.8	13.5	15.9	11.3
Hematocrit (percent)	60.8	40.5	43.2	-	48.2	43.0	35.9	28.0	44.3	40.3	47.0	32.0
WBC ($x10^3/mm^3$)	10.0	14.1	9.4	-	13.1	13.4	7.3	9.4	15.5	24.1	17.2	18.8
Neutrophils (percent)	28	40	27	-	47	65	9	19	23	62	14	13
Bands (percent)	6	19	1	-	10	2	0	3	1	2	1	22
Lymphocytes (percent)	44	25	63	-	27	24	81	77	58	21	71	40
Monocytes (percent)	18	15	7	-	11	7	8	1	6	10	11	11
Eosinophils (percent)	4	1	2	-	5	2	2	0	11	5	3	15
Basophils (percent)	0	0	0	-	0	0	0	0	0	0	0	0
RBC ($x10^6/mm^3$)	6.55	4.48	5.21	-	5.57	4.83	4.29	3.09	3.79	3.43	5.06	4.08
Reticulocytes												
(percent	1.9	0.9	1.1	-	1.6	0.9	1.5	3.4	1.6	0.9	2.4	1.2
($x10^3/mm^3$)	124	40	58	-	83	43	52	105	61	31	121	49
(percent[a])	2.8	0.8	1.4	-	2.3'	1.2	1.7	3.1	1.7	0.8	3.6	1.2

a - corrected for hematocrit as determined by the age of the patient[39]
b - sample not obtained
Formula for correcting reticulocyte count: (Hct(low normal) - Subject's Hct) X Reticulocyte count (%)

TABLE 7. PRE AND POST CEFOPERAZONE LABORATORY RESULTS.

Patient												
SGOT (IU)	33	24	24	-[c]	24	21	20	16	18	16	26	17
SGPT (IU)	12	10	10	-	6	13	15	15	7	8	15	11
ALKP (IU/L)[B]	201	183	159	-	202	176	178	167	148	131	430	402
GGPT (IU/L)	65	68	3	-	4	9	20	16	28	27	60	53
LDH (IU/L)	519	434	256	-	228	254	214	174	300	290	221	208
Total Bilirubin (mg/dl)	8.3	5.5	0.7	-	0.7	0.7	0.6	0.3	3.7	1.6	0.4	0.3
Total Protein (g/dl)	5.0	5.2	6.4	-	5.5	6.7	5.3	5.2	4.8	4.6	4.7	4.0
Albumin (g/dl)	2.7	2.8	4.1	-	3.7	3.4	3.7	3.2	3.1	2.9	2.9	2.5
Serum Creatinine (mg/dl)	0.4	0.4	0.4	-	0.5	0.4	0.3	0.4	0.5	0.6	0.4	0.3
Prothrombin Time (seconds)[a]	10.8/ 11.4	12.0/ 11.0	-	-	10.0/ 10.9	11.6/ 11.3	11.0/ 11.3	10.7/ 10.8	11.9/ 11.5	-	-	-

a - patient/control
b - during rapid growth phases, higher levels than normal may be seen
c - sample not obtained
SGOT - serum glutamic oxaloacetic transaminase (5-40)
SGPT - serum glutamic pyruvic transaminase (5-40)
LDH - lactic acid dehydrogenase (120-300)
Serum Creatinine (0.3-1.0)
Total Protein (6.3-7.5 0-2 months; 4.7-6.7 3-6 months; 4.8-7.0 7-24 months)
GGPT - gamma glutamyl transpeptidase (<206 0-1 month; <71 2-4 months; <37 4-7 months; <22 7 months-10 years)
Total Bilirubin (0.1-1.4 after month; up to 12.0 during the first month

TABLE 8. PRE AND POST CEFOPERAZONE URINALYSIS.

Patient	1		2		3		4		5		6	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Appearance	yel/cl	-[a]	-	-	yel/cl	yel/cl	str/cl	yel/cl	yel/cl	yel/cl	str/cl	yel/cl
pH	5.0	-	-	-	5.5	5.5	7.0	7.0	7.0	6.0	6.0	6.0
Specific gravity	1.002	-	-	-	1.002	1.005	1.003	1.003	1.002	1.006	1.008	1.004
Glucose	0	-	-	-	0	0	0	0	0	0	0	0
Acetone	0	-	-	-	0	0	0	0	0	0	0	0
Protein	0	-	-	-	0	0	0	0	0	0	0	0
Casts/HPF	0	-	-	-	0	rare	0	0	0	0	0	0
RBC/HPF	0	-	-	-	0	rare	0	0	0	0	6	0
WBC/HPF	rare	-	-	-	occs.	rare	occs.	0	0	0	4-6	0
Epithelial cells/HPF	rare	-	-	-	0	0	occs.	0	0	0	2-4	0
Bacteria/HPF	0	-	-	-	0	rare	0	0	0	0	0	0
Urobinogen	wnl	-	-	-	wnl	wnl	0.1	0	wnl	wnl	0.1	wnl

wnl - within normal limits
occs. - occasional
yel - yellow
cl - clear
HPF - high power field
a - sample not obtained
str - straw

TABLE 9. SUSCEPTIBILITY OF CLINICAL ISOLATES TO AMPICILLIN, METHICILLIN, NAFCILLIN, AND TRIMETHOPRIM-SULFAMETHOXAZOLE.[34,35]

	Minimum Inhibitory Concentration (mcg/ml)			
	Ampicillin	Methicillin	Nafcillin	Trimethoprim-Sulfamethoxazole
Staphylococcus aureus	1.6	1.6	0.4	0.4
Staphylococcus epidermidis	0.1	1.6	0.2	0.4
Escherichia coli	5.0	-	-	0.4
Klebsiella pneumoniae	1.25	-	-	0.8
Proteus mirabilis	1.25	-	-	0.8

TABLE 10. SUSCEPTIBILITY OF CLINICAL ISOLATES TO CEFOPERAZONE.[38]

Organism	MIC_{90} (mcg/ml)
Staphylococcus aureus	4
Staphylococcus epidermidis	4
Escherichia coli	1
Klebsiella pneumoniae	2
Proteus mirabilis	1

APPENDIX

CONSENT FORM

CONSENT AND AGREEMENT TO PARTICIPATE AS AN
EXPERIMENTAL SUBJECT IN CLINICAL RESEARCH

Date:_____

Your child will be undergoing a surgical procedure which is routinely treated with antibiotics (your child will receive the routine antibiotics in addition to the new agent, cefoperazone). Antibiotics are used in an effort to prevent infection. Presently two antibiotics are used to achieve the desired treatment. New antibiotics are being developed all the time; cefoperazone is one of these. However, its effectiveness is based on its ability to get into the cerebral spinal fluid (CSF). The concentration of the antibiotic can be measured during the surgical procedure. This would involve nothing out of the ordinary, as serum and cerebral spinal fluid samples are routinely drawn for cultures. In our study, we will use one serum and one CSF sample. We would like to correlate the amount of drug getting into the fluid with the level in the blood at the same time. From this information, we will be able to evaluate this antibiotic's use in the treatment of cerebral infections.

To complete our study, we will need one serum and one CSF sample. Because of the importance of these two samples in the analysis of the antibiotic cefoperazone, we ask your permission to obtain these samples for the benefit of your child, and at no cost to you. You may withdraw your consent for this study at anytime without prejudice.

Medical treatment or compensation for physical injury: In the event you sustain physical injury resulting from the research project in which you are participating, the University of Utah will provide you without charge, emergency and temporary medical treatment not otherwise covered by insurance. Furthermore, if your injuries are caused by negligent acts or omissions of University employees acting in the course and scope of their employment, the University may be liable, subject to limitations prescribed by law, for additional medical costs and other damages you sustain. If you believe that you have suffered a physical injury as a result of participation in this research program, please contact the Office of Research Administration, Phone No. 581-6903.

The above clinical research project in which I have volunteered to participate as an experimental subject has been fully explained to me, and I understand the purpose of the project and the potential benefits to be derived therefrom. I have also had explained to me and fully understand the procedures that will be carried out on my person, and the potential risks and discomforts that are involved. The precautions that will be taken to protect my welfare have been explained to me, and I understand that all possibility of injury cannot be avoided even when these precautions are followed. Nevertheless, I voluntarily assume these risks in order to advance medical knowledge.

I acknowledge that I have had a fair opportunity to ask questions about the above procedures. I understand that I am free to withdraw my consent and to discontinue participation in the project at any

time without prejudice. I agree that data from these experiments may be used for medical and scientific purposes, including publication, with the understanding that my identity will not be revealed unless I expressly consent thereto.

Patient: _____ Signature: _____

If patient is a minor or unable to sign, complete the following in addition to the above:

As legal guardian of the above-named patient, I verify that I understand the nature of these procedures and that I am legally authorized to sign for this patient.

Patient is a minor _____, _____ _____
(age) Signature of Parent or Guardian

Patient is unable to sign because: _____

_____
Signature of Legal Guardian

Hospital No.: _____ Witness: _____

Responsible Investigator's Signature: _____

Protocol No. and Title: _____

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3. Keucher TR, Mealey J: Long-term results after ventriculo-atrial and ventriculo-peritoneal shunting for infantile hydrocephalus. Journal of Neurosurgery. 1979;50:179-186.
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methicillin, cephalothin, and cephaloridine in experimental pneumococcal meningitis. Journal of Laboratory and Clinical Medicine. 1969;73:535-543.

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CURRICULUM VITAE

Mary Elizabeth Gross

PERSONAL DATA

Date of Birth:	November 20, 1957
Place of Birth:	Chicago, Illinois
Marital Status:	Single
Licensure:	Registered Pharmacist, Illinois 051-033352 Registered Pharmacist Intern, Utah 01354-1702-5

ADDRESS

Home:	621 Medical Plaza Salt Lake City, UT 84112
College:	Department of Pharmacy Practice University of Utah Salt Lake City, UT 84112 (801) 581-5941

EDUCATIONAL BACKGROUND

Doctor of Pharmacy Degree
University of Utah, College of Pharmacy
Salt Lake City, Utah
June, 1982

Graduate Gerontology Certificate
University of Utah
Salt Lake City, Utah
May, 1982

Bachelor of Science in Pharmacy
Drake University, College of Pharmacy
Des Moines, Iowa
May, 1980

EDUCATIONAL EXPERIENCE

Residency in Clinical Pharmacy, Chief Resident
Department of Pharmacy Practice
University of Utah, College of Pharmacy
Salt Lake City, Utah
June, 1982

Duties: Teaching (clerkship, didactic), clinical rotations, night call, cardiac arrest team participation, journal club, clinical seminars, committee meetings.

Chief Resident Responsibilities:

- establishing and maintaining the on-call schedule
- scheduling clinical pharmacy residents to observe the Investigational Review Board and Pharmacy and Therapeutics Committees
- scheduling journal club participation for residents, fellows, and faculty
- serve as a liason between administration, faculty, and residents

Committees:

Member, Doctor of Pharmacy Committee. This committee oversees and coordinates the Doctor of Pharmacy/Clinical Pharmacy Residency program.

Clinical Rotations:

Adult Internal Medicine	(12 weeks)
General Surgery	(6 weeks)
Adult Nephrology	(6 weeks)
Adult Infectious Disease	(6 weeks)
Adult Cardiology	(6 weeks)
Family Practice	(6 weeks)
Ambulatory Care - Pediatrics/Geriatrics	(6 weeks)
Geriatrics	(9 weeks)
General Pediatrics	(6 weeks)
Hyperalimentation	(3 weeks)
Drug Information	(6 weeks)
Obstetrics and Gynecology	(6 weeks)
Psychiatry	(6 weeks)
Hospital Pharmacy Management	(3 weeks)

PROFESSIONAL EXPERIENCE

August 1980 - June 1982: Part-time staff, Intermountain Poison Control Center, University of Utah Medical Center, Salt Lake City, Utah -

PROFESSIONAL EXPERIENCE (Continued)

August 1980 - June 1982: (continued)	provide telephone toxicology consults; consult on treatment in emergency room cases; provide a learning atmosphere for students during clerkship training periods in the PCC.
Jan. 1973 - July 1980:	Pharmacy apprentice, Gross Pharmacy, Chicago, Illinois - filling and compounding prescriptions; patient profiles; inventory control; charge accounts.
Sept. 1979 - May 1980:	Pharmacy intern, Urbandale Pharmacy, Urbandale, Iowa - filling and compounding prescriptions; patient profiles; inventory control; McPike's computer system.
June 1979 - Jan. 1980:	Pharmacy technician, Little Company of Mary Hospital, Evergreen Park, Illinois - filling and compounding prescriptions; unit dose, patient profiles, IBM computer system; IV admixtures.

TEACHING EXPERIENCE

"Bacterial Food Poisoning," and "The Management of Snake Bites." Presented for the Advanced Clinical Toxicology course for the first year Doctor of Pharmacy candidates, University of Utah, Spring, 1982.

Toxicology Teaching Fellowship, University of Utah. Responsibilities included the development and implementation of a clinical toxicology course for the first year Doctor of Pharmacy candidates, Spring, 1982.

"DVT and PE," "Hypertension," and "The Treatment of Hypertension." Presented for the Diseases and Drug Therapy course to undergraduate pharmacy students, University of Utah, Winter, 1982.

"Management of DVT and PE." Presented for the Advanced Pharmacotherapeutics course to the first year Doctor of Pharmacy candidates, University of Utah, Winter, 1982.

"Diabetes in the Elderly" and "Hypertension in the Elderly." Presented for the Drug Use in the Elderly course to undergraduate pharmacy students, University of Utah, Winter, 1982, and Spring, 1981.

Teaching Assistant, Adult Internal Medicine, Pediatrics, Obstetrics and Gynecology, Drug Information, Ambulatory Care, Family Practice and Geriatric clerkships, University of Utah, for fifth year pharmacy students.

LABORATORY EXPERIENCE

Jan. 1979 - May 1979	Biopharmaceutical Assay for Aspirin, under Dr. Sidney Finn, Drake University.
Jan. 1979 - May 1979	Pharmacological research under Dr. Gary Russi, Dr. William Teppert, and Dr. Mark Winston, Drake University. Studies included: A comparison of narcotic and non-narcotic analgesics in mice; the effect of nicotine and caffeine on the rat heart; the use of succinylcholine, tubocurarine, and neostigmine in mice.
Sept. 1979 - May 1978	Colchicine study in mice under Dr. Ralph Trottier, Drake University.

RESEARCH PROJECTS

The Penetration of Cefoperazone into the Ventricular Fluid in Patients with Non-Inflamed Meninges. Mary E. Gross, B.S. Pharm., Kelly D. Mutchie, Pharm.D., Principle Investigator, Douglas K. Kelsey, M.D., Ph.D., and James C. Overall, Jr., M.D. Funded by Pfizer Laboratories for $6,000.

Ibuprofen and Skin Test Inhibition in the Elderly: A Pilot Study. Mary E. Gross, B.S. Pharm., Principle Investigator, Martin D. Higbee, Pharm.D., and James S. Wood, M.D. Funded by the Upjohn Company for $2,000.

A Prospective Comparison of the Incidence of Thrombocytopenia and/or Hypertransaminasemia in Patients Receiving Either Beef Lung or Porcine Intestinal Mucosal Heparin. Investigators: John Russo, Jr., Pharm.D., George Dukes, Jr., Pharm.D., Steven Sanders, Pharm.D., Glenn Warden, M.D., Jeffrey Saffle, M.D. Research Assistant, July 1981 to June 1982.

CONTRIBUTED PAPERS/PRESENTATIONS

Gross, M.E., Illsley S., Evaluation of activities of clinical pharmacy residents. Western States Conference for Pharmacy Residents and Preceptors. April, 1982.

PUBLICATIONS

Gross, M.E., Dukes, G.E.: Comparison of beta-adrenergic blockers. Trends in Drug Therapy 3(4):1-4, 1982.

Quan, M.P., Gross, M.E.: Ketoconazole: A new oral antifungal agent is admitted to the formulary. Drugs in Patient Care 5(1): 1-2, 1982.

PUBLICATIONS (Continued)

Gross, M.E., Quan, M.P.: Ketoconazole. Utah Society of Hospital Pharmacists Newsletter 3(4):5-6, December 1981.

Gross, M.E.: Influenza vaccine 1981-1982. Drugs in Patient Care 4(4):15, 1981.

Gross, M.E.: Bromocriptine is added to the formulary. Drugs in Patient Care 4(3):11, 1981.

Gross, M.E.: Laetrile. Iowa Methodist Medical Center Pharmacy Newsletter 11(1):3, 1980.

INVITED PRESENTATIONS

"The medical aspect of aging," ninth grade students, Highland High School, Salt Lake City, May 1982.

"Antacids - an update," Geriatric Treatment and Evaluation Unit, Veteran's Administration Medical Center, Salt Lake City, May 1982.

"The management of osteomyelitis," Infectious Disease Grand Rounds, University of Utah Medical Center, April 1982.

"Patient Monitoring," Utah Society of Hospital Pharmacists Clinical Conference, March 1982.

"Hepatic metabolism of antibiotics," Medical Residents' Noon Conference, Veteran's Administration Medical Center, Salt Lake City, March 1982.

"Ketoconazole: Therapeutic considerations," Dermatology Conference, University of Utah Medical Center, January 1982.

"New cardiac drugs," Coronary Care Unit Nursing Staff, LDS Hospital, December 1981.

"A review of cephalosporins and their use in patients with altered renal function," Nephrology Staff, University of Utah Medical Center, September 1981.

"Cholestasis associated with hyperalimentation," Medical Staff, Newborn Intensive Care Unit, Primary Children's Medical Center, August 1981.

"Geriatric psychopharmacology," Medical Staff, Psychiatric Unit, University of Utah Medical Center, May 1981.

"Mixing of prescription drugs," Mothers Inc. (YWCA), Salt Lake City, April 1981.

INVITED PRESENTATIONS (Continued)

"Lithium therapy: Nephrogenic effects," Medical Staff, Psychiatric Unit, University of Utah Medical Center, April 1981.

"Medication in the elderly," Senior Citizen Health Fair, Salt Lake City, March 1981.

"The harmful effects of mixing over-the-counter preparations," Garden Arts Club, Salt Lake City, February 1981.

"Streptokinase: Review and its use in pregnant women," University of Utah Medical Center Obstetrics and Gynecology Grand Rounds, February 1981.

"Insulin therapy in the pregnant diabetic," Utah State Department of Health Maternal and Infant Care Diabetic Class, January 1981.

"Using medication wisely," Tooele Senior Citizens Group, January 1981.

"Using medication wisely," Grantsville Senior Citizens Group, January 1981.

"Antihistamines - toxicology and treatment," Medical Staff, Pediatric Clinic, University of Utah Medical Center, December 1980.

"Drug induced orthostatic hypotension," Medical Staff, Geriatric Treatment and Evaluation Unit, Veteran's Administration Medical Center, Salt Lake City, December 1980.

"Acetaminophen update," Ramsey Nursing Home Staff, Des Moines, February 1980.

PROFESSIONAL AFFILIATIONS AND ACTIVITIES

Gerontological Society of America, 1982 - present
American Society of Hospital Pharmacists, 1980 - present
American Pharmaceutical Association, 1975 - present
Utah Society of Hospital Pharmacists, 1980 - present
Illinois Pharmaceutical Association, 1975-1980
Student American Pharmaceutical Association, 1975-1980
- Treasurer, Drake University Chapter, 1978-1979
- Corresponding Secretary, Drake University Chapter, 1977-1978
- Coordinator for Drake University in the Greater Des Moines Diabetes Bike-A-Thon, 1976 and 1977

HONORS AND ACHIEVEMENTS

Grace P. Swinyard Memorial Scholarship, University of Utah, College of Pharmacy, 1981
Student American Pharmaceutical Association Outstanding Member, Drake University Chapter, 1980
Drake University College of Pharmacy Faculty Award, 1980
Drake University Student Government Presidential Award, 1980
Outstanding Young Women of America, 1980
Who's Who in Colleges and Universities, 1979
Rho Chi Society, Drake University Chapter, President, 1979
Mortar Board, Treasurer, 1978
American Diabetes Citation, 1977
Alpha Lambda Delta honor society, 1975
Phi Eta Sigma honor society, 1975